Update

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60-second summary

Use this article as part of your CPD to help establish patients on the most suitable treatment package.

Are atypical antipsychotics still a first-line choice?

These drugs are now considered no more effective or tolerable than the earlier typical antipsychotics. Although less likely to cause disabling extrapyramidal effects, the atypicals can cause other troublesome adverse reactions.

Why may there be reluctance to prescribe clozapine?

It can cause a life-threatening decrease in white blood cells so needs strict, and possibly impractical, monitoring regimes. However, it may be the only drug to relieve symptoms, particularly aggression, in difficult-to-treat patients.

Which adverse effects need special vigilance?

Fever, muscle rigidity, fluctuating consciousness and sweating could indicate neuroleptic malignant syndrome.

This article (Module 1523) can help in the following CPD competencies: G1a, G1c, G1d, G1e, C1a, C1c, C3e.
See http://tinyurl.com/68ox7b

Schizophrenia

Helping patients adhere to long-term management plans

Ajay Karia, Laura Kravitz and Chetan Shah

Schizophrenia affects around one in every 100 people during their lifetime. First symptoms are typically experienced between the ages of 15 and 35, and the disease affects men and women equally. Incidence is higher in cities, and in migrant and ethnic minority groups.[2]

Schizophrenia is a psychiatric disorder that alters an individual's perception, thoughts, affect and behaviour.[3] It can often be distressing for individuals and their family, and can influence their personal, social and occupational lives. Early and accurate diagnosis, intervention and the selection of effective treatment(s) are paramount in improving quality of life.

Symptoms

The symptoms of schizophrenia are typically categorised into positive and negative types.

Hallucinations (including auditory and visual), delusional beliefs, behavioural problems and thought disorder form the positive symptoms and would be most prominent during the acute phase of the illness. These are often referred to as the psychotic symptoms of schizophrenia.

Negative symptoms include lack of motivation, energy and emotions, distortions of thought and speech, and social withdrawal. These symptoms are typical of the chronic phase of schizophrenia. They can be difficult to treat with medicines, but can be helped by psychological interventions.

The European criteria for diagnosing schizophrenia are outlined by the World Health Organization in the International Classification of Diseases, 10th edition.[4]

What causes schizophrenia?

The causes of schizophrenia are not fully understood. It is thought that individuals possess different levels of vulnerability determined by a combination of genetic, psychological, social, environmental and biochemical factors.[3]

Biochemical theories include the disruption of various neurotransmitter pathways such as glutamate, serotonin and gamma-aminobutyric acid (GABA). However, most research and treatments focus on blockade of the overactive D_2 dopamine receptors in the brain's pre-frontal cortex, in particular the mesolimbic area. Elevated dopamine levels can interrupt important cognitive, motor and emotional functions, leading to the psychotic symptoms of schizophrenia.

Drug treatment

Since their introduction in the 1950s, antipsychotics remain the mainstay of treatment. They predominantly (or partially with respect to aripiprazole) block D_2 dopamine receptors in the mesolimbic area of the brain, thereby lowering dopamine concentrations.

There is little difference in efficacy between the available antipsychotics, apart from clozapine, which is licensed for treatment-resistant schizophrenia, but they are categorised into 'typical' and 'atypical' based primarily on their pharmacology and side effect profiles.

Typical antipsychotics ('first generation') act with similar efficiency by predominantly blocking D_2 dopamine receptors. However, they differ in their ability to block other receptors, such as histamine and cholinergic receptors, thus producing diverse adverse effect profiles. Typical antipsychotics are usually associated with increased extrapyramidal side effects (EPSE) and sedation.

Atypical or second generation antipsychotics block dopamine receptors more selectively than typical antipsychotics, decreasing the likelihood of EPSE. Furthermore, their novel pharmacology in blocking serotonin 2a receptors was initially thought to contribute to the atypical antipsychotics' greater efficacy on the negative symptoms of schizophrenia and their more tolerable side effect profiles. However, recent studies suggest that this binding is unrelated to the efficacy or adverse effect profile, and again raise uncertainty about their exact mode of action.[3]

Adverse effects

The adverse effects of antipsychotics can be predicted according to the individual drug's pharmacology. Dopamine blockade in areas of the brain other than the mesolimbic area can give rise to adverse effects. Dopamine blockade in the nigrostriatal pathway is thought to produce EPSE. Similarly, dopamine blockade in the tuberoinfundibular pathway causes raised prolactin levels (leading to sexual dysfunction and menstrual irregularities) and dopamine blockade in the mesocortical pathway gives rise to cognitive side effects.

EPSE can be particularly troublesome and include parkinsonian symptoms (including tremor), akathisia (restlessness), dystonia (abnormal face and body movements) and dyskinesia, and tardive dyskinesia (rhythmic,

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involuntary movements of tongue, face and jaw). These adverse effects significantly contribute to the reduced quality of life suffered by patients.

Antipsychotics' effect on different receptors also cause other side effects such as dry mouth, blurred vision, constipation, urinary retention (cholinergic blockade), sedation (histamine blockade), postural hypotension, dizziness and syncope (alpha antagonism).

Table 1 (in the full version of this article online at www.chemistanddruggist.co.uk/update) describes the adverse effects of commonly used antipsychotics and exhibits their heterogeneity.

Choice of antipsychotics

Until recently, Nice had recommended atypical antipsychotics as the first-line treatment in people with newly diagnosed schizophrenia and for patients already prescribed typical antipsychotics for whom treatment response was inadequate or who suffered adverse effects.[7] However, in March 2009 the advice was rephrased to state that the choice of antipsychotic drug should:

- be made in discussion with the patient
- take into account the views of the carer
- reflect the degree of sedation required

The relative potential of individual antipsychotic drugs to cause EPSE, metabolic side effects (including weight gain and cardiovascular problems) and other adverse effects such as unpleasant subjective experiences should also be taken into consideration.[3,8]

This was in direct response to emerging evidence that atypical antipsychotics do not possess greater efficacy or tolerability than typical antipsychotics. Although atypical antipsychotics have a lower propensity to induce EPSE, they nevertheless have an adverse effect profile of their own that can significantly affect the individual's morbidity and mortality.[3, 9, 10]

Table 2 (in the full version of this article online at www.chemistanddruggist.co.uk/update) outlines choice of antipsychotics when certain side effects are particularly troublesome.

Treatment resistant schizophrenia

Clozapine is a unique atypical antipsychotic in that it is recognised as being particularly effective when conventional agents have failed. It is documented to reduce the risk of suicide in schizophrenia and is especially useful for quelling violence and aggression in difficult cases.[11]

Clozapine's mode of action involves antagonism of dopamine and serotonin receptors, but it is unclear why the drug has a higher level of efficacy. In contrast, it can produce life-threatening and potentially fatal agranulocytosis, a condition involving a dangerous fall in white blood cells.

Regular (initially weekly) blood tests and registration for healthcare professionals and patients with the clozapine monitoring service are mandatory before supply can be made. Clozapine can also increase the risk of seizures, cause weight gain, diabetic keto-acidosis and possibly has the greatest cardiometabolic risk among the antipsychotics.

Nice guidance states that clozapine should be offered to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs, one of them being a non-clozapine second-generation antipsychotic.[3] However, in practice the initiation of treatment with clozapine is often delayed unnecessarily, probably because of its impractical monitoring regimes (for needle-phobic or patients in whom oral adherence cannot be assured) and the fear of side effects.

Formulations

Antipsychotics can be administered orally or by long-acting depot injections. Where oral administration is not suitable, for example for those patients who cannot reliably remember to take their treatment, a long-acting intramuscular 'depot' formulation that can be injected at weekly, fortnightly or monthly intervals may be desirable.

In addition to liquid preparations, oral dispersible formulations that dissolve on the tongue or disperse in drinks are also available. They can be taken under supervision, so are particularly useful if the patient is non-adherent with the medication.

Points to note

There is no benefit in prescribing more than one antipsychotic at the same time and could cause significant harm.

Particular care should be taken when treating patients with dementia, pre-existing or history of cardiovascular disease, stroke, epilepsy, diabetes and Parkinson's disease, and the elderly.

Treatment packages should include regular electrocardiogram (ECG) and biochemical testing (liver function test abnormalities, electrolyte imbalances, full blood counts, plasma glucose, prolactin and lipid levels), together with a review of the patient's physical health status (eg weight, blood pressure) and drug adverse effects. Following baseline assessments at the initiation of treatment, these tests should be repeated every six to 12 months.[3]

Non-pharmacological treatment

Psychological and psychosocial interventions can be used to reduce symptoms, increase insight, prevent relapse and to promote adherence. Cognitive behavioural therapy (CBT), family interventions and art therapy are particularly highlighted by Nice.[3] CBT attempts to allow individuals to manage their thoughts and behaviour in order to control their symptoms, and should be offered to all patients with schizophrenia.

Family interventions provide education and support for those who are close to the patient, allowing them to manage problems effectively. In addition, art therapy aims to promote creative expression and is particularly effective for managing or reducing negative symptoms. These interventions are especially useful when medicines do not fully relieve symptoms.

Counselling

It is important for patients to realise that schizophrenia can be a lifelong condition. Adherence to treatment packages is of the upmost importance and pharmacists must provide support to ensure treatment meets the patient's needs. Treatment interventions have to be effective and without unwanted side effects.

Patients should be encouraged to discuss their illness and treatment beliefs to improve adherence. Counselling on weight management, alcohol use, driving, smoking, complementary treatments and over the counter medications is useful.

Patients should be educated on how their medication works, administration regimes, drug interactions and side effects to improve adherence. In particular, patients should be told to report unexplained symptoms, especially fever, muscle rigidity, fluctuating consciousness and sweating that resemble the rare, but potentially fatal side effect of antipsychotics known as neuroleptic malignant syndrome. Support should be given to the family, and information on non-drug treatments and support groups is valuable.

Summary

The management of schizophrenia involves a comprehensive care package that often includes pharmacological treatment. Treatment adherence is of great importance and patients must be educated to ensure they engage in their treatment. For this long-term treatment to be successful clinicians must also engage with the treatment and illness beliefs of patients and their carers.

References are available in the full version of this article online at www.chemistanddruggist.co.uk/update

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Further Information

1. Mind. Online at www.mind.org.uk. A UK mental health charity that focuses on various psychiatric illnesses.

2. Rethink. Online at www.rethink.org. Also a national charity focusing on mental illnesses and provides information on support groups.

NEXT WEEK
Update discusses the management of angina

Schizophrenia

Reflect

What are the positive symptoms of schizophrenia? How do typical antipsychotics work? What are the side effects of atypical antipsychotics? What problems are associated with clozapine?

Plan

This article describes the symptoms, causes and treatment of schizophrenia. It includes information about typical and atypical antipsychotics, and their adverse effects. It also discusses treatment with clozapine and non-drug treatments.

Act

- Find out more about the symptoms, causes and treatment of schizophrenia from the Royal College of Psychiatrists' website at http://tinyurl.com/schizophrenia-1.
- Read more about cognitive behavioural therapy and how it can help patients with schizophrenia on the Royal College of Psychiatrists' website at http://tinyurl.com/bm4x7m.
- Revise your knowledge of the different drugs and formulations available by reading the BNF section 4.2.1 on antipsychotic drugs.
- Find out more about neuroleptic malignant syndrome from the Patient UK website at http://tinyurl.com/murs9b.

Evaluate

Are you now confident in your knowledge of the symptoms and causes of schizophrenia? Are you familiar with the drugs used in its treatment and their side effects? Could you give advice to patients and carers about schizophrenia?

5 minute test
What have you learned?

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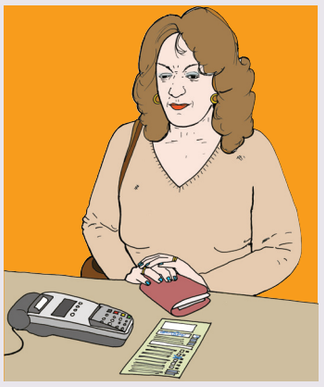
Practical Approach | Test yourself in this everyday pharmacy scenario

Do you need to agree with exemption claims?



Locum pharmacist Salma Hussain is working in a pharmacy in a deprived area. She is at the prescription reception area one morning when a woman comes in with two prescriptions. The woman signs the declaration on the reverse of the first one that she is receiving income support and claiming exemption. Salma asks her if she has anything to show that she is receiving the benefit. The woman looks irritated and says: "No, not on me. And anyway, they've never asked me for anything here before."

Salma takes the script and ticks the 'evidence not seen' box. The woman starts to sign the exemption declaration on the second prescription. She asks Salma which box she should tick.

"Who is it for?" Salma asks.

"My son."

"How old is he?"

"Eighteen."

"Is he at school or college?"

"No, he's got a full-time job."

"Well," says Salma, "I'm afraid that you're going to have to pay the prescription charge. There are three items here, so it's £21.60."

"What!" retorts the woman. "We can't afford to pay that! I'm just going to tick that he's on jobseeker's allowance."

Before Salma can say anything more the senior sales assistant, who has been listening to the conversation, intervenes and says to Salma: "This is a very poor area. The owner says that we can't deprive our customers of medicines they need if they can't afford to pay the prescription charge. He says that it's not our responsibility to check if their exemption declarations are correct. We just tick the 'evidence not seen' box and dispense the script."

Questions

1. Do pharmacy staff have a responsibility to verify that a patient's declaration of exemption is genuine?

2. Is it morally right to turn a blind eye to a false declaration of exemption entitlement if a patient genuinely cannot afford to pay?

Answers

1. PSNC's views (for England) and the RPSGB's appear to conflict. PSNC states: "Where patients do not have evidence or where there is doubt over whether the evidence provided is genuine or appropriate, the 'evidence not seen' box on the back of the prescription should be marked with an X by pharmacy staff. Pharmacy staff should not refuse to dispense items on the basis that the patient does not provide evidence of their entitlement to free prescriptions. Pharmacy contractors are in no way responsible for the accuracy of a patient's declaration; this remains the responsibility of the patient." (www.psnc.org.uk/pages/points_of_dispensing_checks_guidance.html)

However, the RPSGB states: "Pharmacists are reminded to check that the declaration on the back of the prescription form has been filled in correctly... where a patient (or his or her representative) declares an exemption from prescription charges, the pharmacist is required to check for evidence of this… a false declaration made by the pharmacist, whether knowingly or as a result of failure to check a patient's exemption, may constitute a criminal offence or professional misconduct or both." (www.rpsgb.org.uk/pdfs/LEBpreventNHSfraud.pdf)

2. This question is best answered by those practising at the frontline – send comments to haveyoursay@chemistanddruggist.co.uk

This article can help with these CPD competencies: Gih, G1j,G3e, G4a, C5a.
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Do you have an idea for a Practical Approach scenario or would you like to write one? Email us at: **haveyoursay@chemistanddruggist.co.uk**

Table 1: The incidence of adverse effects of some antipsychotics and available formulations

(Adapted from Psychotropic Drug Directory 2010, Stephen Bazire, and The Maudsley Guidelines 10th Edition 2009)[5,6]

Drug	EPSE	Weight gain	Prolactin elevation	Anti cholinergic	Postural hypotension	Sedation	Cardiac
Typical antipsychotics							
Chlorpromazine (o)	++	+++	+++?	+++	+++	+++	++
Flupentixol (o/d)	++	+	++?	++	_	+	_
Fluphenazine (d)	++	+	+++?	++	+	++	++
Haloperidol (o/i/d)	+++	+	+++	+	+	+	++
Pipotiazine (d)	++	?	+++?	++	+	+	++
Sulpiride (o)	+	+	++	+	_	+	_
Trifluoperazine (o)	++	?	+++?	-	+	+	++
Zuclopentixol (o/d)	+++	+?	++?	++	+	++	+
Atypical antipsychotics							
Amisulpride (o)	+	+	++	_	_	_	_
Aripiprazole (o/i)	_	+	_	_	_	_	+
Clozapine (o)	_	+++	_	+++	+	+++	+++
Olanzapine (o/i)	_	+++	+	+	_	++	_
Quetiapine (o)	_	+	+	+	+	+	+
Risperidone (o/d)	+	+	++	_	+	+?	_

Side effects
+++ marked effect ++ moderate effect + mild/transient effect – little or minimal effect
? No information or little reported

Formulations available:
o = oral i = short-acting injection d = long-acting intramuscular depot injection

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Table 2. Choice of antipsychotics to manage certain adverse effects

(Adapted from The Maudsley Prescribing Guideleines 10th Edition 2009)[6]

Adverse effect	Suggested drug	Alternatives
Acute EPSE	Aripiprazole, quetiapine, olanzapine	Clozapine, risperidone (less than 6mg/day)
Hyperprolactinaemia (raised prolactin)	Aripiprazole,* quetiapine	Clozapine, olanzapine
Weight gain	Amisulpride, haloperidol, trifluoperazine, aripiprazole*	Quetiapine, risperidone
Tardive dyskinesia	Clozapine	Olanzapine, quetiapine, aripiprazole
Impaired glucose tolerance	Amisulpride, aripiprazole*	Risperidone
QT prolongation	Aripiprazole (with ECG monitoring)	Any low dose monotherapy with ECG monitoring
Sedation	Amisulpride, aripiprazole, risperidone, sulpiride	Haloperidol, trifluoperazine
Postural hypotension	Amisulpride, aripiprazole, Sulpiride, haloperidol, trifluoperazine	

* There is evidence that both switching to and co-prescription of aripiprazole is effective in reducing weight, prolactin and in reversing impaired glucose tolerance.

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